The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 19 October 2000
CPMP/BPWG/198/95 rev.1

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF HUMAN PLASMA DERIVED FACTOR VIII AND IX PRODUCTS

DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	June 1999
TRANSMISSION TO THE CPMP	June 1999
RELEASE FOR CONSULTATION	June 1999
DEADLINE FOR COMMENTS	December 1999
DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	May 2000
TRANSMISSION TO THE CPMP	May 2000
RELEASE FOR TWO MONTHS' CONSULTATION (only on the change in the repeat pharmacokinetics and the new recommendation for a post-marketing study)	June 2000
FINAL ADOPTION BY THE CPMP	October 2000
DATE FOR COMING INTO OPERATION	April 2001

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (+44-20) 74 18 84 00 Fax: (+44-20) 74 18 85 45
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

CLINICAL INVESTIGATION OF HUMAN PLASMA DERIVED FACTOR VIII AND IX PRODUCTS

Table of contents

1. INTRODUCTION

Before 1960 plasma was the only agent generally available for the treatment of the hereditary coagulation disorders. Several plasma product concentrates are now available for this purpose, which have been purified and virally inactivated using various principles. In factor VIII and factor IX deficiency, replacement therapy consists of factor VIII/IX products of different purity. The recognition in the mid-1980's that coagulation factor concentrates had caused widespread transmission of human immunodeficiency virus (HIV) and non-A non-B hepatitis (now recognised as mainly hepatitis C) resulted in major changes to manufacturing processes in order to introduce steps to inactivate or remove these and other blood-borne viruses. However, occasional incidents of transmission of these and other blood-borne viruses have still occurred in recent years, and measures designed to minimise contamination of the starting plasma and to maximise the elimination of blood-borne viruses during production are essential to ensure the virological safety of plasma-derived products. In view of outbreaks of hepatitis A among haemophiliacs treated with a solvent detergent factor VIII in 1992 and later, the Committee on Proprietary Medicinal Products (CPMP) approved the position paper of the Biotechnology Working Party (III/5830/93) on blood products and non-enveloped viruses, recommending that the manufacturing process should include a viral inactivation/removal step which is also effective against non-enveloped viruses. This recommendation was further developed by revision of the CPMP notes for guidance on viral validation and on plasma-derived products (Note for Guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95, February 1996) and Note for Guidance on plasma-derived products (CPMP/BWP/269/95, revision 1 March 1996). Changes in the manufacturing procedures may lead to significant changes in the product, and may thereby alter the structure of the coagulation factor and its activity.

The occurrence of an antibody against factor VIII, a so-called inhibitor, is the most important complication in haemophilia treatment. Inhibitors occur in up to about 30% of patients with severe haemophilia A, usually within the first 100 exposure days. These inhibitors have mainly been observed in previously untreated children, and approximately one third disappeared on continued treatment with the same product. It now appears that in cases in whom inhibitors occur, patient related factors (certain types of mutations in the factor VIII gene, the family history, ethnicity, possibly HLA-DR constitution) appear to be more important determinant of inhibitor development than the product.

Two inhibitor 'outbreaks' occurred in the early 1990's in previously tolerant patients who had been treated for a number of years following exposure to plasma-derived products subjected to a modified virus inactivation method. Hence, the incidence of inhibitor formation may be affected by the specific product used for treatment and its potential to result in alteration of factor VIII molecules, 'neoantigens'. It was apparent from this experience that the risk of inhibitor formation related to an individual product could be evaluated in previously treated patients (PTPs). Previously untreated patients (PUPs) should not be used for study of product related immunogenicity of concentrates, since patients with a high degree of previous exposure appear to be a better suited study population.

Clinical trial data, addressing efficacy and safety with respect to immunogenicity and other adverse events, are required in an application for a marketing authorisation. In addition, the potential for thrombogenicity should be investigated in the case of factor IX products. This Note for Guidance describes the clinical trials required for authorisation with respect to human plasma derived factor VIII (pdFVIII) and human plasma derived factor IX (pdFIX) products. These data are required for:

1. products for which an application for a marketing authorisation is to be submitted, referred to as 'new products' in the text and

2. authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures), referred to as 'modified products' in the text.

The clinical trials described in this note for Guidance should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

According to good clinical practice all patients entered into clinical trials should be vaccinated against hepatitis A and B, and evidence of immunisation should be present at baseline.

1.1 Efficacy

In clinically evaluating human plasma derived coagulation factors for the treatment of haemophilia A or B patients, the initial trial typically examines the pharmacokinetics of the principal active factor. Appropriate pharmacokinetic data (incremental recovery, half-life, area under the curve (AUC), mean residence time (MRT) and clearance) are the most important (surrogate) endpoints for efficacy of a new factor VIII/IX product. The International Society on Thrombosis and Haemostasis (ISTH) also provides guidance on pharmacokinetic studies. It could be useful to consult this guidance for advice when designing studies.

1.2 Safety

Safety aspects of factor VIII/IX products include viral safety, immunogenicity and other adverse events. For factor IX products thrombogenicity should also be considered a safety issue.

1.2.1 Adverse events

- All adverse events occurring in relationship with any use of the new product should be recorded and reported.

Product specific:

- Development of hypersensitivity reactions to murine proteins with related adverse reactions

1.2.2 Viral safety

Manufacturers of plasma-derived products, including coagulation factors, are obliged to optimise viral safety by rigorous selection of donors, screening of donations, including testing for HBsAg, antibody to hepatitis C virus, antibody to HIV 1+2 and by using appropriate viral inactivation/removal methods according to the recommendations in the "Note for Guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses" (CPMP/BWP/268/95, February 1996) and "Note for Guidance on plasma-derived products" (CPMP/BWP/269/95, rev. 2, July 1998).

Three principal complementary approaches are adopted to control potential viral contamination of coagulation factor products: selecting and testing source material, testing the capacity of the production process to inactivate or remove viruses, and testing the product at appropriate stages of production, including plasma pool testing for hepatitis C virus RNA by nucleic acid amplification technology (CPMP/BWP/390/97, March 1998).

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

The applicant is still required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue using their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

1.2.3 Immunogenicity

1.2.3.1 Factor VIII products

The occurrence of antibodies against factor VIII is a major complication of haemophilia treatment. The risk of inhibitor occurrence is higher in patients with severe haemophilia A than in patients with moderate and mild disease. Inhibitor risk may be associated with commencing or changing treatment or where the antigenicity of the product has been altered due to changes in the manufacturing process. Previously treated patients are the most suitable candidates to test the product-related immunogenicity of a factor VIII product.

1.2.3.2 Factor IX products

Haemophilia B is around 4 times less common than haemophilia A. The incidence of inhibitors in these patients following administration of factor IX is less common compared to the incidence found in haemophilia A patients. Inhibitors to factor IX have been demonstrated in approximately 4% of patients with severe haemophilia B. In the case of purified factor IX products, the immunogenicity should be investigated prior to their authorisation. It has been observed that the occurrence of inhibitors is commonly associated with the total deletion of the factor IX gene. Unlike those with haemophilia A, patients with haemophilia B often experience anaphylactic reactions to factor IX products in association with the development of inhibitors. Literature also reports on the occurrence of anaphylactic type reactions as well as the development of a nephrotic syndrome following immune tolerance therapy. These problems have been observed for plasma-derived as well as for recombinant factor IX products.

1.2.4 Thrombogenicity (factor IX products)

Treatment with pdFIX products that contain factors II, VII and X has been associated with thrombosis. Factor IX products with higher purity have displayed less risk of thrombogenicity. For all new factor IX products, tests for markers of activation of coagulation should be carried out in post-infusion samples obtained in the non-bleeding state.

2. PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED: 'NEW PRODUCTS'

2.1 Clinical trials with new human plasma derived factor VIII products

2.1.1 Efficacy

A pharmacokinetic trial should be performed in at least 12 subjects suffering from haemophilia A (factor VIII ≤1%). The study should record incremental recovery, *in vivo* half-life, area under the curve (AUC), clearance and mean residence time (MRT) in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of product for at least 3 days (7 days if possible). Samples for factor VIII activity determination should be taken before injection of 25-50

IU/kg of the factor VIII product and at 10-15, and 30 minutes, 1, 3, 6, 9, 24, 28 and 32 hours after the infusion; 48 hours sample is optional. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak level recorded within the three hours after infusion and reported as [IU/ml]/[IU/kg].

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation.

Clinical efficacy after administration should be assessed from the clinical response as reported by patients in the safety trials. Clinical efficacy should be assessed by calculating the consumption of factor VIII, expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand, and surgery). Response should be assessed as "none", "moderate", "good" or "excellent" by the physician for those patients who were treated in hospital with the product for major bleeds. In addition, response will be determined by the physician in a minimum of 5 patients undergoing at least 10 surgical procedures, including efficacy of haemostasis, loss of blood, and requirements for transfusion.

Continuous infusion

At the time of this Note for Guidance, bolus injection of factor VIII has been the standard treatment in haemophilia A patients. Continuous infusion therapy has not been authorised in the EU. If this mode of administration is requested, clinical data are required to establish its efficacy and safety. A suggested protocol is described below.

The study should be carried out in at least 12 severe haemophilia A (FVIII ≤1%) patients undergoing elective major surgical procedures

Prior to surgery, a pharmacokinetic analysis in each individual (as described in these guidelines) should be performed to obtain, in particular, an estimate of clearance. The initial infusion rate should then be based on the clearance as follows:

Clearance x desired steady state level = infusion rate (IU/kg/hr)

Efficacy and safety data during surgery and for at least 6 days thereafter should be submitted, including:

- PK parameters (clearance, distribution volume) with the description of the method used;
- Description of the administration rate;
- Daily dosage of factor VIII with the description of the method used;
- Blood loss;
- Transfusion requirements;
- Local and systemic side-effects.

Pharmaceutical data on reconstitution and stability of the product should be provided in Part II.

Immune tolerance

Any request for an indication of induction of immune tolerance in haemophilia A patients with inhibitors should be accompanied by clinical data.

2.1.2 Safety

Clinical safety will be assessed in all patients receiving the factor VIII product:

- in patients included in the pharmacokinetic trial: blood pressure, heart rate, temperature, respiratory rate and adverse events
- in all patients participating in the clinical trials: adverse events.

All adverse events should be recorded and reported in accordance with the ICH guideline "structure and content of clinical study reports" (CPMP/ICH/137/95E3)

2.1.3 PTPs (Previously treated patients) study

Choice of patients

In view of the fact that PTPs may be evaluated for product related immunogenicity, a larger number of patients than specified in the previous Note for Guidance need to be included in the studies. These PTPs above 12 years of age, with factor VIII ≤2% should be immunocompetent (CD4 lymphocytes >400/µl) with at least 150 treatment exposure-days to previous products. At least 50 patients should be followed for at least 50 exposure days or 6 months whichever is sooner. These data should be provided with the application. Where patients are only rarely treated during a 6-month period (i.e. less than 10 total exposure days) they will not count towards the total number studied for immunogenicity, but should be included for other parameters of safety.

Immunogenicity testing

The factor VIII inhibitor titre should be determined at baseline and every 3 months. In the clinical studies, it is proposed to perform sampling for inhibitor measurements not less than 3 days after the previous administration, if possible. For all patients who develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative incidence and the number of exposure days. The titre of the inhibitor should be reported in Bethesda Units (BU) using the modified assay.[1] Plasma samples of patients who are suspected of inhibitors or who have developed inhibitors should be stored for possible future testing.

Viral safety

Compliance with CPMP recommendations with regard to viral safety under 1.2.2 is necessary for all plasma derived products and is verified by information supplied in Part II of the dossier.

A pre-treatment serum sample from each patient included in the clinical trials should be stored at -70˚C for possible future testing.

2.1.4 Treatment of PUPs (Previously untreated patients)

The product-related immunogenicity is more adequately addressed through studies of PTPs rather than PUPs. As stated in section 1.2.2, it is no longer considered appropriate to use clinical trials to investigate viral safety. For these reasons and since only a limited number of PUPs are available, there is no formal requirement for a PUP study to be carried out, but all treatment of PUPs and all adverse events should be documented. Experience with PUPs should be stated in the SPC.

Treatment in PUPs should not be initiated until data are available on 50 exposures for 20 patients (older than 12 years) who are included in the PTP trial.

2.1.5 Treatment of children

Since children may respond differently compared to adults, an open multicentre trial should include at least 20 children under the age of six years regardless of prior treatment. The

1 Giles AR, Verbruggen B, Rivard GE, Teitel J, Walker I. A detailed comparison of the performance of the standard versus the Nijmegen modification of the Bethesda assay in detecting factor VIII:C inhibitors in the haemophilia A population of Canada. Association of Hemophilia Centre Directors of Canada. Factor VIII/IX Subcommittee of Scientific and Standardization Committee of International Society on Thrombosis and Haemostasis. Thromb-Haemost. 1998 Apr; 79(4): 872-5

children should be tested for inhibitors every 3 months or if there is any suspicion of inhibitor development. The factor VIII consumption (dose/kg for prophylaxis and therapy (on demand)) should be monitored as well as development of inhibitors. The trial should not be started until data are available on 50 exposures for 20 patients (older than 12 years) who are included in the PTP trial. The study should continue until the patients have received at least 50 exposures to the product or have been treated for 6 months whichever is sooner. For all patients who develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative incidence and the number of exposure days in relation to development of inhibitors. The titre of the inhibitor should be reported in Bethesda Units, using the modified assay. Plasma samples from patients who are suspected of inhibitors should be stored for possible future testing.

This study may be submitted after a marketing authorisation is granted. The number of children treated should be reflected in the SPC. Until such a study has been carried out, the SPC should include a statement that there are insufficient data to recommend the use of the product in children less than 6 years of age.

2.1.6 Post-marketing study

To ensure consistency in the long-term between data from the clinical studies and from routine use, a post-marketing study should be undertaken and a protocol submitted with the dossier. The results of the PTP study should be taken into account in the design of this study.

2.2 Clinical trials with new human plasma derived factor IX products

2.2.1 Efficacy

A pharmacokinetic trial, should be performed in at least 12 subjects suffering from haemophilia B (factor IX ≤2%). The study should record incremental recovery, *in vivo* half-life, area under the curve (AUC), clearance and mean residence time (MRT) in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of product for at least 4 days (7 days if possible). Samples for factor IX activity determination should be taken before injection of 50-75 IU/kg of the new factor IX product and 10-15, and 30 minutes, 1, 3, 6, 9, 24, 48 and 50 hours after the infusion; 72 hours sample is optional. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak level recorded within the three hours after infusion and reported as [IU/ml]/[IU/kg].

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis. Patients taking part in the pharmacokinetic trial should continue treatment with the product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation.

Clinical efficacy after administration should be assessed from the clinical response as reported by patients in the safety trials. The clinical efficacy should also be evaluated by calculating the consumption of factor IX, expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand and surgery). Response should be assessed as “none”, “moderate”, “good” or “excellent” by the physician for those patients who were treated in hospital with the product for major bleeds. In addition, response will be determined by the physician in a minimum of 5 patients undergoing at least 10 surgical procedures, including efficacy of haemostasis, loss of blood and requirement for transfusion.

Continuous infusion

At the time of this Note for Guidance, bolus injection of factor IX has been the standard treatment in haemophilia B patients. Continuous infusion therapy has not been authorised in the EU. If this mode of administration is requested, clinical data are required to establish the efficacy and safety. A suggested protocol is described below.

The study should be carried out in at least 10 severe haemophilia B (FIX ≤2%) patients undergoing elective major surgical procedures.

Prior to surgery, a pharmacokinetic analysis in each individual (as described in these guidelines) should be performed to obtain, in particular, an estimate of clearance. The initial infusion rate should then be based on the clearance as follows:

Clearance x desired steady state level = infusion rate (u/kg/hr)

Efficacy and safety data during surgery and for at least 6 days thereafter should be submitted, including:

- PK paramenters (clearance, distribution volume) with the description of the method used;
- Description of the administration rate;
- Daily dosage of factor IX with the description of the method used;
- Blood loss;
- Transfusion requirements;
- Local and systemic side-effects.

Pharmaceutical data on reconstitution and stability of the product should be provided in Part II.

2.2.2 Safety

In addition to the requirements for factor VIII products (see 2.1.2), appropriate tests for activation of coagulation (prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer) should be carried out after administration of the product. This should be determined in the patients participating in the pharmacokinetic trial. Clinical evaluation of thrombosis should be undertaken by safe, objective means in a minimum of 5 patients undergoing at least 10 surgical procedures. .

In patients developing anaphylaxis and/or inhibitors to factor IX, data on IgE as well as IgG1, IgG2, IgG3 and IgG4 against factor IX (using appropriate methods) should be submitted.

2.2.3 PTP study

Please refer to requirements for factor VIII products (see 2.1.3). Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of previously treated patients followed up for immunogenicity may be lower than for factor VIII products: 20 patients.

The titer of the inhibitor should be reported in Bethesda Units (BU), using the Bethesda assay.

2.2.4 Treatment of PUPs

See 2.1.4

2.2.5 Treatment of children

See 2.1.5

Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of previously treated patients followed up for immunogenicity may be lower than for factor VIII products: 12 patients.

2.2.6 Post-marketing study

See 2.1.6

3. CHANGE IN THE MANUFACTURING PROCESS OF AUTHORISED PRODUCTS: 'MODIFIED PRODUCTS'

3.1 Introduction

Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the coagulation factor and its activity. The effects of changes in the manufacturing process (e.g. viral inactivation steps or purification procedures) on the biological characteristics and activity of the product should be investigated. If significant impact on the activity of the coagulation factor cannot be excluded, data on pharmacokinetics, efficacy and safety should also be provided with the application.

The currently available factor VIII preparations differ with respect to purity and method of viral inactivation/removal. Until recently, the evidence supporting the hypothesis that a particular production process is associated with a higher than normal risk of inhibitor induction has been very limited. Two inhibitor outbreaks occurred in the early 1990's in previously tolerant patients who had been treated for a number of years following exposure to a plasma-derived product subjected to a modified virus inactivation method. Hence the incidence of inhibitor formation may be affected by the type of product used for treatment and its potential to result in alteration of factor VIII molecules, 'neoantigens'. Such inhibitors will be demonstrable in previously treated patients.

3.2 Clinical trials with human plasma derived modified factor VIII products

3.2.1 Efficacy

Evidence should be provided to demonstrate that the change in the manufacturing process has not affected the pharmacokinetics of the product.

A comparative pharmacokinetic trial should be performed in at least 12 subjects suffering from haemophilia A (factor VIII ≤1%). The study should record incremental recovery, *in-vivo* half-life, area under the curve (AUC), clearance and mean residence time (MRT) in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of the product for at least 3 days (7 days if possible). Samples for factor VIII activity determination should be taken before injection of 25-50 IU/kg of the factor VIII product and 10-15, and 30 minutes, 1, 3, 6, 9, 24, 28 and 32 hours after the infusion; 48 hours sample is optional. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak level recorded within the three hours after infusion and reported as [IU/ml]/[IU/kg].

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation.

Should any of the patients participating in the clinical trials undergo surgical procedures, response will be determined by the physician, including efficacy of haemostasis, loss of blood and requirement for transfusion.

3.2.2 Safety

Please refer to requirements for new human plasma derived factor VIII products. (See 2.1.2)

3.2.3 PTP study

See 2.1.3

3.2.4 Post-marketing study

See 2.1.6

3.3 Clinical trials with human plasma derived modified factor IX products

3.3.1 Efficacy

Evidence should be provided to demonstrate that the change in the manufacturing process has not affected the pharmacokinetics of the product.

A comparative pharmacokinetic trial should be performed in at least 12 subjects suffering from haemophilia B (factor IX ≤2%). The study should record incremental recovery, *in-vivo* half-life, area under the curve (AUC), clearance and mean residence time (MRT) in patients without inhibitors who are not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of product for at least 4 days (7 days if possible)**.** Samples for factor IX activity determination should be taken before injection of 50-75 IU/kg of the new factor IX product and 10-15, and 30 minutes, 1, 3, 6, 9, 24, 48 and 50 hours after the infusion; 72 hours sample is optional. At least 3 different lots should be employed in the trial. Incremental recovery is determined as the peak level recorded within the three hours after infusion and reported as [IU/ml]/[IU/kg].

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the product for 6 months, and should be re-tested for the same pharmacokinetic parameters after 3-6 months using the same dose as in the first investigation.

Should any of the patients participating in the clinical trials undergo surgical procedures, response will be determined by the physician, including efficacy of haemostasis, loss of blood, requirement for transfusion and occurrence of thromboembolic episodes.

3.3.2 Safety

In addition to the requirements for factor VIII products (see 2.1.2), appropriate tests for activation of coagulation (prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer) should be carried out after administration of the product. This should be determined in the patients participating in the pharmacokinetic trial. Clinical evaluation of suspected incidences of thrombosis should be undertaken by safe, objective means in any patients undergoing surgical procedures.

In patients developing anaphylaxis and/or inhibitors to factor IX, data on IgE as well as IgG1, IgG2, IgG3 and IgG4 against factor IX (using appropriate methods) should be submitted.

3.3.3 PTP study

See 2.1.3 and 2.2.3

3.3.4 Post-marketing study

See 2.1.6

Clinical trials with human plasma derived factor VIII products: new products

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia A patients (factor VIII ≤1%) without inhibitors and not actively bleeding.	1. Pharmacokinetics	Incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be re-tested after 3-6 months.
	2. Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events.
5 haemophilia A patients undergoing at least 10 surgical procedures.	1. Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor VIII consumption.
	2. Safety	Adverse events.
PTP study 50 PTPs (>12 years) (factor VIII ≤2% and CD4>400/µl).	1. Clinical efficacy	Factor VIII consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor titre in Bethesda Units, using the modified assay, at baseline and every 3 months, at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events.
Treatment of PUPs.	All treatment of PUPs should be documented.	
Open multicentre trial in 20 children with haemophilia A (<6 years) to be started after results of 50 exposures in 20 PTPs (>12 years) have become available.	1. Clinical efficacy	Factor VIII consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor testing every 3 months or if there is any suspicion of inhibitor development. Continue until at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events
Post-marketing study.	1. Clinical efficacy	Protocol should be provided.
	2. Immunogenicity	
	3. Safety	

Clinical trials with human plasma derived factor VIII products: modified products

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia A patients (factor VIII ≤1%) without inhibitors and not actively bleeding.	1. Pharmacokinetics	Comparative trial: incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be tested again after 3-6 months.
	2. Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events..
Any haemophilia A patients undergoing surgical procedures.	1. Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor VIII consumption.
	2. Safety	Adverse events.
PTP study 50 PTPs (>12 years) (factor VIII ≤2% and CD4>400/µl).	1. Clinical efficacy	Factor VIII consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor titre in Bethesda Units, using the modified assay, at baseline and every 3 months, at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events..
Post-marketing study.	1. Clinical efficacy	Protocol should be provided.
	2. Immunogenicity	
	3. Safety	

Clinical trials with human plasma derived coagulation factor IX products: new products

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia B patients (factor IX ≤2%) without inhibitors and not actively bleeding.	1. Pharmacokinetics	Incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be re-tested after 3-6 months.
	2. Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.
5 haemophilia B patients undergoing at least 10 surgical procedures.	1. Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor IX consumption.
	2. Safety	Adverse events. Thrombogenicity.
PTP study 20 PTPs (>12 years) (factor IX ≤2% and CD4>400/µl).	1. Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor titre in Bethesda Units at baseline and every 3 months, for at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events.
Treatment of PUPs.	All treatment of PUPs should be documented.	
Open multicentre trial in 12 children with haemophilia B (<6 years) to be started after results of 50 exposures in 20 PTPs (>12 years) have become available.	1. Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor every 3 months or if there is any suspicion of inhibitor development. Continue until at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events.
Post-marketing study	1. Clinical efficacy	Protocol should be provided
	2. Immunogenicity	
	3. Safety	

Clinical trials with human plasma derived coagulation factor IX products: modified products

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
12 haemophilia B patients (factor IX ≤2%) without inhibitors and not actively bleeding.	1. Pharmacokinetics	Comparative trial: incremental recovery, half-life, AUC, clearance and mean residence time. Patients should be tested again after 3-6 months.
	2. Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events. Thrombogenicity.
Any haemophilia B patients undergoing surgical procedures.	1. Clinical efficacy	Efficacy of haemostasis, loss of blood and requirement for transfusion. Factor IX consumption.
	2. Safety	Adverse events. Thrombogenicity.
PTP study. 20 PTPs (>12 years) (factor IX ≤2% and CD4>400/µl).	1. Clinical efficacy	Factor IX consumption, physician's assessment of response in treatment of major bleeds.
	2. Immunogenicity	Inhibitor titre in Bethesda Units at baseline and every 3 months, for at least 50 exposure days or 6 months' treatment.
	3. Safety	Adverse events..
Post-marketing study.	1. Clinical efficacy	Protocol should be provided.
	2. Immunogenicity	
	3. Safety	